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Adverse effects of concomitant somatic symptoms on the course of depressive and anxiety symptoms: a secondary analysis of a Randomized Clinical Trial in the primary care setting

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Abstract:

Background: The majority of patients suffering from anxiety and depression receive treatment in the primary care setting. In that setting, the concomitant somatic symptoms that often occur might influence the course of anxiety and depression. This has not yet been the subject of extensive research, but it might be of high clinical relevance.

Aim: To study the effects of concomitant somatic symptoms on the course of depressive and anxiety symptoms.

Methods: Secondary data-analysis of a Randomized Clinical Trial assessing the effectiveness of problem solving treatment for depressive and anxiety symptoms, compared with care as usual in primary care. Somatic symptoms were measured at baseline with the PHQ15. Severity of depressive and anxiety symptoms was assessed with the HADS. Logistic regression analysis was used to determine the effect of the PHQ15 score on the outcome.

Results: The PHQ15 score proved to be a predictor for a negative course of depressive and anxiety symptoms. The odds ratio for a negative course was 2.12 per increase of one standard deviation (4.7 points) on the PHQ-15. This association was similar in both treatment groups in the trial.

Conclusions: Concomitant somatic symptoms were a strong predictor of a poor outcome in both treatment groups in the trial. This implies a generic effect of somatic symptoms on the effectiveness of commonly applied treatments for depressive and anxiety symptoms. Further research is needed to explore this phenomenon and the effectiveness of adapting treatments to the needs of patients with concomitant somatic symptoms.

Background

Symptoms of depression and anxiety are a burden to patients and society as a whole⁶, and the vast majority of patients suffering from these symptoms are treated in primary care.¹⁷² Apart from pharmacotherapy, a number of psychosocial treatments have been developed and evaluated in this setting, such as Cognitive Behavioral Therapy (CBT)¹⁷³⁻¹⁷⁵ and Problem Solving Treatment (PST).^{61;62;176;177} So far, however their effectiveness in the primary care setting has been less than expected, based on the outcomes of efficacy studies carried out in specialized mental health settings.¹⁷⁸⁻¹⁸⁰ Given the high prevalence of depression and anxiety in primary care, this may be an important issue.

The cause of this limited effectiveness does not appear to be a lack of feasibility of the treatments provided in primary care. PST, for instance, was specifically designed for the time-constrained primary care setting.¹⁷⁶ It is therefore important that factors that might modify the effectiveness of treatment are identified. One of the factors that might modify the effectiveness of CBT, PST and other such interventions is the co-occurrence of somatic symptoms, as measured with commonly used questionnaires such as the Patient Health Questionnaire (PHQ)¹⁴¹, in patients with depressive and anxiety symptoms.

This is by no means a rare phenomenon in primary care. In one study, 70% of the depressed patients presented somatic symptoms instead of psychological symptoms to their general practitioner (GP) during their first visit.²⁵ Somatic symptoms accompanying depressive and anxiety symptoms might therefore be an expression of cosyndromality. In other words, they could be an expression of a depressive or anxiety disorder, with symptoms across the physical-mental spectrum.¹⁸¹ They might also be an independent factor indicating somatization¹⁸²⁻¹⁸⁴, because somatization, depression and anxiety can overlap considerably, although each make an independent contribution to aspects of impairment.¹⁸⁵

Apart from this scientific evidence, it is also a clinical opinion that somatic symptoms can interfere with the course and outcome of depressive and anxiety symptoms. The development and recent evaluation in primary care of Diagnostic Criteria for Use in Psychosomatic Research (DCPR)¹⁸⁶ underlines the fact that the importance of somatic symptoms is also recognized in general practice. However, the magnitude of the impact of somatic symptoms on the course and treatment of depressive and anxiety symptoms in primary care has not yet been established.

For the present study we hypothesized that concomitant somatic symptoms in primary care patients with depressive and anxiety symptoms would predict a poor course and a poor treatment outcome. Since a study¹⁶⁵ comparing enhanced care for depression with care as usual (CAU) suggested that enhanced care only has surplus value for psychological presenters and not for physical presenters, our second hypothesis was that the effect of physical symptoms would be stronger for patients receiving psychotherapy than for patients receiving CAU. Both hypotheses were tested in a secondary analysis of data from a recently completed Randomized Clinical Trial (RCT) which assessed the effectiveness of PST compared to CAU in primary care.¹⁸⁰

Methods

Design and participants in the main study

The main study was a RCT assessing the effectiveness of PST for symptoms of depression and anxiety, compared to CAU, in 12 general practices in and around Amsterdam. The design¹⁷⁷ and results¹⁸⁰ of this RCT have been published elsewhere. 175 patients who scored positive on at least 3 out of 12 questions on the General Health Questionnaire 12 (GHQ-12) and who had visited their GP three or more times in the previous six months participated in the study. Patients were included in the present analysis if they had filled out the Hospital Anxiety and Depression scale (HADS; $n=130$) at baseline and at follow-up (after three months). In addition the MINI neuropsychiatric interview was administered, which provides diagnostic information on the presence of DSM-IV diagnoses.⁷⁴ Patients were not excluded if they did not meet the diagnostic criteria for one of these disorders, neither was the diagnosis of such a disorder an inclusion criterion.

Patients in the intervention group received up to six sessions of PST provided by trained nurses. The nurses were closely supervised, and before they started treating patients in the RCT they treated four patients to practice their skills. In the CAU group the GPs provided care that was intended to be as natural as possible^{177;180}, for which many GPs adhere to the guidelines issued by the Dutch College of General Practitioners.^{11;177}

After 9 months the patients in the CAU group had paid slightly more visits to their GP: 4.8 versus 4.1. They had also paid more visits to an outpatient clinic (4.2 versus 2.3), and had more often been visited by home carers (7.9 hours versus 4.2). Admission to a secondary care facility was also more common in the CAU group: 1.3 days versus 0.3 days. On average, the CAU group paid 1 visit to a psychologist during the trial, compared with 1.1 visit in the PST group. Apart from the attendance of 5 sessions of PST in the intervention group, none of the differences in other aspects of care were significant.¹⁸⁷

Outcome

The effects of the intervention were evaluated at three months follow-up. The primary outcome measure was the total HADS score. This questionnaire consists of 14 items on a 0-3 scale, thus generating a score between 0 and 32. Higher scores indicate more symptoms of depression and anxiety.¹⁸⁸ Improvement was defined as a 50% decrease in total symptom-level on the HADS after three months. An unfavourable course was defined as an improvement of less than 50% on the HADS three months after inclusion. A 50% reduction in symptom-level is a commonly used cut-off point to define a clinically relevant response to treatment.⁵⁹

Operational definition of somatic symptoms

In the present study somatic symptoms were measured with the PHQ15³⁰, which consists of 15 somatic symptoms derived from the Patient Health Questionnaire (PHQ).¹⁴¹ Each symptom is scored from 0 ("not bothered at all") to 2 ("bothered a lot"). Adding up the scores for the individual items creates a total score between 0 and 30, and this score is the independent variable in the present secondary data-analysis. The PHQ15 evaluates 90% of the somatic symptoms reported in the outpatient setting.³⁰

Analysis

A multiple logistic regression analysis was performed, with the aim to assess the association of the PHQ15 total score at baseline with improvement on the HADS after

three months. For this purpose, all participants for whom a HADS score after three months was present were entered in the analysis, regardless of the outcome of the randomization process.

The analysis was adjusted for severity on the HADS at baseline, gender, ethnicity and age. Additional information was available on two DSM-IV diagnoses at baseline, namely depression and hypochondriasis. All participating patients were assessed for these diagnoses with the MINI.⁷⁴ Even though DSM-IV diagnoses might be associated with a high score on the HADS at baseline, they might still also have an independent influence on the relationship between physical symptoms and the outcome. In order to investigate this possibility, these variables were entered in the model. Information was also available on whether or not psychopharmacological treatment was initiated between baseline and the end of the treatment phase (i.e. after three months). Therefore, this variable was also entered in the model.

The second aim of our study was to assess whether or not a possible effect of somatic symptoms (measured with the PHQ15 at baseline) on the course of depressive or anxiety symptoms was different for patients who received PST than for patients who received CAU. In order to investigate this possibility of effect-modification by type of treatment, the interaction term 'randomization status times PHQ15 score' was added to the logistic regression model. The commonly used critical P-value of 10% was used to assess whether or not there was a significant interaction.

Results

Patient characteristics

After being screened, 175 patients were included in the trial (i.e. 21.1% of those who screened positive). 144 patients also completed the baseline HADS. 14 patients did not complete the HADS at follow up, and because the HADS at follow up was the primary outcome measure we started the present analysis with 130 patients. The patients who did not complete the HADS at follow up scored slightly higher on the HADS and the PHQ15 at baseline, but these differences were not significant. Based on the number of 175 patients who were randomized, the total drop-out percentage for the present analysis was 25.7%. Drop-out was 21% in the CAU group and 31% in the PST group, with no significant difference between the groups with regard to age or gender. The flowchart showing the number of participants who completed each step can be found in Figure 1. Baseline characteristics and outcomes at three months are presented in Table 1.

Results of the regression analysis

The results of the logistic regression analysis are shown in Table 2. The odds ratio (OR) on an unfavourable course measured with the HADS is 1.17 per point increase on the PHQ15 at baseline (95% CI: 1.019-1.351). One standard deviation (SD=4.7) of the PHQ15 score at baseline would imply an OR for an unfavourable course of 2.12 (95% confidence interval (CI): 1.09-4.11). This means that in our study sample the odds on an unfavourable course of depressive and anxiety symptoms is twofold greater for patients who score approximately 5 points higher on the PHQ15 (scores from 0 to 30) than for patients with a score that is 5 points lower.

The OR changed, but remained significant after adjustment for a number of variables, such as the baseline severity of the HADS and diagnoses of MDD and/or hypochondria as determined with the MINI.

Figure 1. Flowchart of the RCT

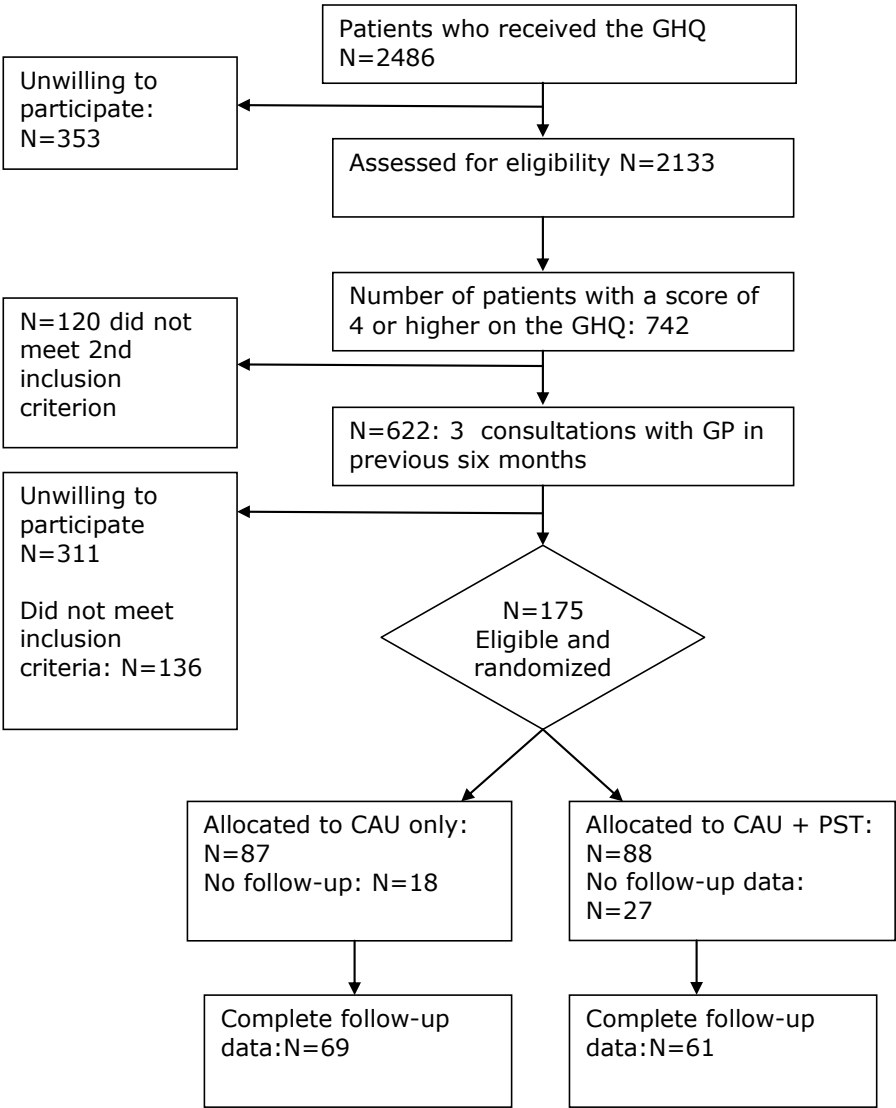


Table 1. Characteristics of participants

Baseline	PST	CAU	Total
	N=61	N=69	N=130
Age M (SD)	53.3 (14.4)	52.5 (15.1)	52.8 (14.7)
HADS at T0 M (SD)	15.1 (7.1)	16.5 (7.1)	15.7 (7.2)
PHQ15 at T0 (SD)	9.9 (4.8)	10.7 (4.3)	10.3 (4.7)
Diagnosis of MDD	17 (28.8%)	16 (23.2%)	33 (25.8%)
Diagnosis of hypochondria	6 (10.2%)	12 (17.4%)	18 (13.8%)
Female gender	45 (76.3)	48 (69.6)	93 (72.7)
Ethnicity other than Dutch	8 (13.6)	10 (14.5)	18 (14.1)
T1 (after 3 months)			
HADS at T1 M (SD)	12.1 (7.1)	14.0 (7.6)	13.0 (7.4)
HADS difference at T1 M (SD)	3.1 (6.7)	2.7 (5.5)	2.9 (6.1)
Percentage of patients who responded at T1 ¹	25.9%	16.2%	20.6% (P=.181) ²
Percentage of patients taking psychotropic medication between T0 and T1	30.9%	28.4%	29.0% (P=.629) ²
¹ Response was defined as a 50% decrease in total symptom-level on the HADS after three months. ² Two-sided Pearsons Chi square for difference between groups.			

Adding the interaction term 'randomization status times PHQ15 score' to the logistic regression model described above resulted in no significant improvement ($P=.823$). There is therefore no reason to assume that the association of concomitant somatic symptoms with the course of symptoms of depression and anxiety is stronger or weaker in either the PST group or the CAU group.

Table 2. Results of the logistic regression analysis with response on the HADS at T1 as outcome variable

PHQ15 and variables adjusted for	Beta	Standard Error	Odds Ratio (OR)	P-value	CI OR (95%)*	
					lower bound	Upper bound
• PHQ15	.160	.072	1.173	.027	1.019	1.351
• HADS at baseline	-.023	.047	.977	.626	.891	1.072
• Gender (female)	-.294	.531	.746	.580	.263	2.110
• Ethnicity (non Dutch)	1.411	1.086	4.101	.194	.488	34.452
• Age	-.019	.018	.981	.293	.947	1.016
• MDD	.520	.782	1.683	.506	.363	7.789
• Psychotropic medication	-.561	.555	.571	.312	.192	1.694
• Hypochondriasis	.228	.757	1.257	.763	.285	5.538
• Constant	-.161	2.479	.851	.948	.007	109.710

*Confidence Interval of the Odds Ratio

Discussion

This secondary data-analysis provides clear evidence for a negative association between the level of somatic symptoms and the course of depressive and anxiety symptoms in primary care. The higher the score on the PHQ15 (a scale for somatic symptoms that commonly co-occur with mental health problems) the less likely a patient was to experience at least a 50% symptom reduction on the HADS. The odds ratio for such an unfavourable course was 2.12 per standard deviation on the PHQ15 (4.7 points).

There was no significant interaction between randomization status (PST or care as usual) and the PHQ15 score. Since there were no significant differences between the two groups with regard to the treatment that was provided, except for the 5 sessions of PST, the conclusion must be that the association between somatic symptoms and the course of symptoms of depression and anxiety is the same for both treatment modes. This implies that there appears to be a generic negative influence of somatic symptoms on the effectiveness of treatment for symptoms of depression and anxiety in primary care.

In our opinion, there are two likely explanations for this negative effect. First of all, concomitant somatic symptoms could be an expression of the severity of depressive or anxiety symptoms. If this had been the case, the effect of somatic symptoms should have disappeared after adjustment for baseline severity on the HADS and a diagnosis of MDD according to the MINI-Neuropsychiatric interview. However, this was not the case, and thus does probably not explain the effect of somatic symptoms that was found.

The second possible explanation is that concomitant somatic symptoms are an independent factor, such as somatization, with a negative impact on the course of depressive and anxiety symptoms. If this was the case for the patients in the RCT we studied, the effect of somatization could have been due to hypochondria. Following this line of reasoning, the effect of somatic symptoms should then have disappeared at least partly after correction for a diagnosis of hypochondria, but this diagnosis did not have a strong impact.

However, the effect of somatic symptoms could still be an expression of somatization, in the sense that they could be so-called Medically Unexplained Symptoms (MUS), but from the data we used it was not possible to distinguish between somatic symptoms with a clear medical explanation and MUS. It is therefore unclear whether the somatic symptoms measured with the PHQ15 in the RCT reflect true somatization, or whether they are the result of comorbid medical conditions. Future studies should establish whether or not this distinction is relevant. Either way, the present data suggest that concomitant somatic symptoms in patients with depression and anxiety are associated with a poorer prognosis.

The importance of the finding that somatic symptoms are associated with a poorer outcome of symptoms of depression and anxiety, becomes clear when one realizes that most patients who are depressed report somatic symptoms instead of psychological symptoms during their first visit to a GP.¹⁸¹ Both psychological and pharmacological interventions have been found to be efficacious in the treatment of MDD, but it is often difficult to replicate these results in everyday practice.^{178;179;189} PST is no exception to this rule.^{178;180} In our opinion, a major challenge for the future is, therefore, to tailor efficacious forms of treatment for depressive symptoms and anxiety in such a way that they are also effective in primary care. The data from our study show that it might prove

to be well worth while to pay attention to the role of somatic symptoms in the process of tailoring interventions.

A useful tool for this purpose might be the Diagnostic Criteria for use in Psychosomatic Research (DCPR)¹⁹⁰ that has recently been evaluated in primary care.¹⁸⁶ The DCPR classifies 12 psychosomatic syndromes that might play a mediating role in the course and outcome of psychiatric disorders.¹⁹¹ A thorough assessment according to these can be made by a GP alone or together with a consultant-liaison psychiatrist who can also assist with the choice of treatment in primary care. Consultant-liaison models have been found to enhance the effectiveness of treatment in primary care for depression⁵⁶, anxiety¹⁹² and for MUS in primary care.¹⁴ Patients suffering from symptoms of depression and anxiety as well as somatic symptoms might reap the benefits if these services are intensified.

